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Bristol-Myers Squibb Company

December 13, 2004

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004D-0378; International Conference on Harmonization: Draft Guidance on S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals; Availability; *69 Federal Register 55164 (September 13, 2004)*

Dear Sir or Madam:

Bristol-Myers Squibb (BMS), a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, infant formulas, and nutritional products, is pleased to have the opportunity to offer comments on the *Draft ICH S7B Guidance Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals*. Our company's mission is to extend and enhance human life by providing the highest-quality pharmaceutical and related health care products. For this reason, we are interested in commenting on the Draft Guidance. Our comments are set forth below.

Summary of BMS Comments on Proposal

We commend the ICH for drafting guidance to provide recommendations to sponsors concerning nonclinical studies to assess the potential of a drug to cause delayed ventricular repolarization as a predictor of proarrhythmic risk. We recognize the intent to encourage integrated risk assessment of drug effects on ventricular repolarization and the QT/QTc interval as a standard part of drug development. There are, however, aspects of the proposed guidance that require clarification or appear contrary to the ICH's stated objectives, which we have cited below.

Specific Comments

Lines 56-61. General principles for nonclinical studies

Recommendation: The guidance should include a statement on whether the nonclinical studies should be conducted in compliance with the Good Laboratory Practices (GLPs).

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Lines 162-164. "Results from the S7B nonclinical studies assessing the risk for delayed ventricular repolarization and QT interval prolongation generally do not need to be available prior to first administration in humans."

Recommendation: The discussion of the timing of the nonclinical studies is vague. We would suggest that in most cases these studies be conducted prior to first administration in humans for drugs not already in clinical development. The current Draft Guidance on E14 Clinical Evaluation of QT/QTc Interval Prolongation (Docket No. 2004D-0377) states that "whether non-clinical testing can exclude a clinical risk for QT/QTc prolongation is controversial" and goes on to recommend that a "thorough QT/QTc" clinical trial be conducted. If the nonclinical data are not required before that trial, the need for the nonclinical data after such a trial would be questionable.

Lines 209-211. "Species differences in terms of which cardiac ion channels contribute to cardiac repolarization and to the duration of the action potential should be considered in selecting a test system"

Recommendation: A sentence should be added stating that Purkinje fibers from rabbit are extremely sensitive to drug-induced action potential prolongation compared to other species.[1] We've tested a number of positive control IKr inhibitors in both dog and rabbit Purkinje fibers and our data support this. For instance, dofetilide (0.03μM) prolongs rabbit and dog Purkinje fiber APD_{90} by ~130% and 30% at 1Hz, respectively. E-4031 (0.1μM) prolongs rabbit and dog Purkinje fiber APD_{90} by ~75% and 20% at 1Hz, respectively. Early afterdepolarizations, an important proarrhythmia signal, occur more frequently in rabbit than in dog Purkinje fibers with the same concentration of IKr inhibitor.

Lines 269-270. "the most common approach is to correct the QT interval for heart rate (QTc) using formulae such as Bazett or Fredericia....."

Recommendation: Since it is generally recognized that Bazett's correction is inappropriate for dog and cyno, Van de Water's formula could be substituted for Bazett's, or at least included.

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1 Lu HR, Marien R, Saels A et. al. Species plays an important role in drug-induced prolongation of action potential duration and early afterdepolarizations in isolated Purkinje fibers. J Cardiovasc Electrophysiol. 2001;12:93-102.

Line 258-272. Correction of QT interval at varied heart rates.

Recommendation: The guidance document should acknowledge the utility of rate corrections developed for individual subjects using individual QT-RR relationships. This recommendation is based on the following information.

Both population-based rate-corrections (e.g., Bazett's, Fridericia's, Van deWater's, etc.) and subject-based rate correction formulae are used in the clinical and non-clinical safety pharmacology areas. Population based formula are typically used because of their ease of use and because, until recently, data for calculating individual rate correction formulae were not readily available. However, clinical and nonclinical data developed over the last several years demonstrate that QT-RR relationships vary between subjects and that individual subject correction formula most accurately reflect true QTc.[2,3,4,5] Our data show that individual animal correction formulae vary between animals, are stable, and are more accurate than population-based correction formulae in conscious dogs and non-human primate models.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA/ICH give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

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2 Malik M and Camm AJ. Evaluation of drug-induced QT interval prolongation, implications for drug approval and labelling. Drug Safety, 2001. 24(5): 323-351.

3 Batchvarov VN, Ghuran A, Smetana P, Hnatkova K, Harries M, Dilaveris P, Camm AJ, and Malik M. QT-RR relationship in healthy subjects exhibits substantial intersubject variability and high intrasubject stability. Am J Physiol Heart Circ Physiol, 2002. 282: H2356-H2363.

4 Davey P. How to correct the QT interval for the effects of heart rate in clinical studies. J Pharmacological Toxicological Methods, 2002. 48:3-9.

5 Malik M, Hnatkova K and Batchvarov V. Differences between study-specific and subject-specific heart rate corrections of the QT interval in investigations of drug induced QTc prolongation. 2004. Pace. 27:791-800.